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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,839	09/30/2004	Kazuhiro Fukunaga	732964-55670	4338

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EXAMINER	
COTTON, ABIGAIL MANDA	
ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 10/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/509,839	FUKUNAGA ET AL.	
	Examiner	Art Unit	
	Abigail M. Cotton	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9 and 12-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9 and 12-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 21, 2006, has been entered.

Claims 9 and 12-24 are pending in the application and are being examined on the merits herein.

The claims are being rejected as follows.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 9 and 12-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,046,164 to Asano et al, issued April 4, 2000, in view of EP 0 267 015 to Amy L. Finkenaur, published May 11, 1988.

Asano et al. teaches a method for treating diseases of periodontal tissue by administering a basic fibroblast growth factor (see abstract, in particular.) Asano et al. teaches that the bFGF can be prepared in various formulations, including liquids by combining bFGF with a pharmacologically acceptable additive, such as a solvent, stabilizer, etc. (see column 4, lines 4-15, in particular.)

Asano et al. does not specifically teach providing hydroxypropyl cellulose in the bFGF composition, as recited for example in claim 9.

Finkenaur teaches that a stabilizing effective amount of a water-soluble polysaccharide can be provided in medicinal compositions containing a polypeptide growth factor with mitogenic activity to stabilize the polypeptide growth factor against

loss of biological activity in the presence of moisture (see abstract, in particular.) Finkenaur teaches that basic fibroblast growth factor is an example of such as polypeptide growth factor that can be stabilized with the polysaccharide (see page 3, lines 25-30, in particular.) Finkenaur further teaches that the polysaccharides act to increase the viscosity of the composition (see page 4, lines 55-65, in particular), and thus are thickeners. Finkenaur teaches that the stabilizing polysaccharide for stabilizing the polypeptide growth factor can be selected from among polysaccharides including methyl cellulose, hydroxyethylcellulose, hydroxypropyl methylcellulose, and hydroxypropyl cellulose, as in claim 9 (see page 3, lines 35-50, in particular.)

Accordingly, one of ordinary skill in the art at the time the invention was made would have found it obvious to incorporate the hydroxypropyl cellulose stabilizer/thickener of Finkenaur into the bFGF composition taught by Asano et al. and administer for the treatment of periodontal disease, because Asano et al. teaches that a composition comprising bFGF and a stabilizer can be administered for the treatment of periodontal disease, and Finkenaur teaches that polysaccharides such as hydroxypropyl cellulose (that are also thickeners) act to stabilize bFGF. Thus, one of ordinary skill in the art would have been motivated to provide the polysaccharide of Asano et al. in the bFGF composition of Asano et al. for administration with the expectation of administering a stabilized formulation capable of treating periodontal disease. Therefore, the method of claim 9 is obvious over the teachings of Finkenaur and Asano et al.

Regarding claims 12 and 15, Asano et al. teaches that the bFGF composition can treat periodontitis (periodontosis.) Regarding claims 13-14 and 16, Asano et al. teaches that a suitable content of bFGF in the composition can be from 0.001 to 20%, which is the same as the ranges being claimed. Regarding claim 17, Asano et al. teaches that the composition can be administered for repair of periodontal tissue after tooth extraction, and for regeneration of dentin defected by dental caries, as recited in the claim.

Regarding claims 18-19, Asano et al. teaches that the bFGF can be combined with pharmacologically acceptable additives, such as a suspending agent, stabilizer or filling material (see column 4, lines 1-13, in particular), and thus teaches that an inactive and non-toxic additive can be provided. Asano et al. also teaches that the bFGF can be combined with a solvent, and the composition can be prepared by a known method such as dissolution of the bFGF. Finkenaur teaches providing a polysaccharide (thickener) in the composition, as discussed above. Accordingly, the references teach providing the preparation in a solution for dissolution with a thickener and an inactive and non-toxic additive as recited in the claims.

Regarding claims 20-21, Finkenaur teaches the stabilized compositions can be in the form of aqueous medicinal compositions (see page 3, lines 55-60, in particular.)

Regarding the viscosity of the preparation as recited in claims 22-24, it is noted that Finkenaur teaches that the polysaccharide stabilizer can be provided to give a desired viscosity, such as a viscosity in the range of 1-5000 cps (see page 4, lines 55-65, in particular), which overlaps and/or encompasses that claimed. Finkenaur teaches that the increased viscosity improves the residence time of the effective concentration of the growth factor (see page 4, lines 55-64, in particular.) Finkenaur also generally teaches that the amount of cellulose derivative provided can be selected according to the concentration of the growth factor, the type of formulation and the like (see page 3, lines 55-62, in particular.) Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the amount and/or type of the cellulose derivative stabilizing agent provided in the composition, according to the guidance provided by Asano et al. and Finkenaur, to provide a composition having desired stabilization, viscosity and residence time properties. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.)

Response to Arguments

Applicant's arguments filed August 21, 2006 have been fully considered but they are not persuasive.

In particular, Applicants argue that the claimed method of involving administration of a viscous preparation comprising bFGF and the particular polysaccharide that is hydroxypropyl cellulose provides unexpectedly good results. Applicants have presented a declaration under 37 CFR 1.132 and signed by Moriyuki Ohkuma that presents a comparison of the stability of bFGF in solutions having various different polysaccharides and other thickeners, including hydroxypropylcellulose, fibrinogen, sodium carboxymethyl cellulose, hydroxypropylmethylcellulose and methylcellulose. Applicants point out that the thickeners fibrinogen and sodium carboxymethyl cellulose resulted in solutions that had either denatured bFGF or were excessively turbid, and thus could not be measured. Applicants further note that the solution having the claimed polysaccharide, namely hydroxypropyl cellulose, exhibited a loss of bFGF after 24 hours of only about 1.3%, whereas the comparison polysaccharides hydroxypropylmethylcellulose and methylcellulose exhibited a loss after 24 hours of about 5.5% and 7.6%, respectively. Applicants thus assert that the viscous preparation having the particular polysaccharide that is hydroxypropyl cellulose and method of use thereof provides unexpectedly good results, including over the polysaccharides such as methylcellulose and hydroxypropylmethyl cellulose that are taught in the prior art.

The Examiner finds these results unpersuasive. It is noted that evidence of unexpected results must compare the claimed subject matter with the closest prior art to be effective to rebut a prima facie case of obviousness. In re Burckel, 592 F.2d 1175, 201 USPQ 67 (CCPA 1979). In the instant case, Finkenaur discloses that the stability

of growth factors such as bFGF can be enhanced by providing water soluble polysaccharides, and even teaches that "the hydroxyalkyl cellulose derivatives such as hydroxypropyl cellulose, hydroxyethylcellulose and hydroxypropyl methylcellulose are preferred," (see page 3, lines 35-43, in particular) and thus lists the claimed polysaccharide that is hydroxypropyl cellulose amongst those that are particularly preferred. Accordingly, given Finkenaur's teachings of the enhanced stability imparted by the polysaccharides, it is not deemed unexpected that the claimed hydroxypropyl cellulose imparts good stability to the growth factor bFGF, such as better stability that the thickener fibrinogen.

With regards to the magnitude of the stability enhancement for the hydroxypropyl cellulose versus the comparison polysaccharides, namely methylcellulose and hydroxypropyl methyl cellulose, it is noted that Finkenaur teaches the desirability of using *water soluble* cellulose derivatives to impart the stability enhancement, and furthermore teaches that "the solubility of the cellulose derivatives is determined by the degree of substitution (D.S.) of ether groups and the stabilizing derivatives useful in the present invention should have a sufficient quantity of such ether groups per anhydroglucose unit in the cellulose chain to render the derivatives water soluble" (see page 3, lines 44-48, in particular), and thus Finkenaur teaches that the water-solubility and thus stabilization properties of the polysaccharides can vary according to the degree of substitution of the compounds. Furthermore, it is noted that properties such as the length of the polysaccharide can affect the solubility and thus the stabilization

properties of the polysaccharide. Accordingly, the fact that a composition having hydroxypropyl cellulose can be prepared to provide an amount of bFGF that reduces by only about 1.3%, and compositions comprising other such water-soluble polysaccharides (methyl cellulose and hydroxypropyl methyl cellulose) can be prepared that result in a greater loss of bFGF, such as 5.5% and 7.6%, is not considered unexpected, as Finkenaur teaches that the solubility, and thus the stabilization properties of the polysaccharide are dependent upon not only the type of polysaccharide used, but also for example upon the degree of substitution of the polysaccharide. Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the desired polysaccharides, and to optimize and/or adjust the degree of substitution of the polysaccharides, as well as other contributing stability factors such as the polysaccharide molecular weight, to provide a composition having the desired stability. Thus, it is considered that Applicants do not provide sufficient evidence of unexpected results in comparison to the closest prior art. See MPEP 716.02(e).

Furthermore, it is noted that evidence of unexpected results is required to be reasonably commensurate in scope with the claimed invention. See, e.g., In re Kulling, 897 F.2d 1147, 1149, 14 USPQ2d 1056, 1058 (Fed. Cir. 1990); In re Grasselli, 713 F.2d 731, 743, 218 USPQ 769, 777 (Fed. Cir. 1983). Applicants show results for compositions having "hydroxypropyl cellulose" and "hydroxypropyl methylcellulose," for example, but do not specify what particular celluloses are being tested, i.e. to what

degree the celluloses are substituted, the molecular weight of the celluloses, etc, and thus it cannot be determined whether the results are commensurate in scope with the broader class of compounds that falls within the scope of "hydroxypropyl cellulose" in general.

Applicants furthermore argue that the primary reference, Asano et al, does not teach "viscous" bFGF preparations, and thus does not provide sufficient motivation to combine with Finkenaur for the purposes of combining the polysaccharide into the bFGF composition. The Examiner notes that Asano et al. teaches that the bFGF composition can comprise other pharmacologically acceptable additive, such as solvents and stabilizers (see column 4, lines 4-13, in particular), and Finkenaur teaches that the polysaccharides act as stabilizers for growth factors such as bFGF in medicinal compositions (see abstract, in particular.) Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the polysaccharide of Finkenaur in the bFGF composition of Asano et al, with the expectation of providing a pharmacologically acceptable stabilizer in the composition.

Applicants also argue that Finkenaur does not specifically disclose the treatment of periodontal disease with the growth factors. The Examiner notes that the Asano et al. reference is being relied on for the teaching of the administration of bFGF for the treatment of periodontal disease, whereas Finkenaur teaches that the polysaccharides

are suitable for medicinal preparations, which is a category that includes dental treatments. It is noted one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abigail M. Cotton whose telephone number is (571) 272-8779. The examiner can normally be reached on 9:30-6:00, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AMC

SREENI PADMANABHAN
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